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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,648	12/19/2001	Henrik Bisgard-Frantzen	4318.234-US	8501

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,648	BISGARD-FRANTZEN ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-33,35 and 37-47* is/are pending in the application.

4a) Of the above claim(s) *40-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-33 35 37* is/are rejected.

7)☒ Claim(s) *38 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-29, 34, and 36 have been canceled. Claims 30-33, 35, and 37-47 are still at issue and are present for examination.

Applicants' arguments filed on 1/16/04, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 40-47 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the response filed 4/24/03.

Claims 30-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of variants of a parent α-amylase having at least 80% identity to the parent α-amylase and four specific mutations (i.e., deletion of residues

equivalent to 179 and 180 of SEQ ID NO:3, and substitutions of the residues equivalent to 349 and 428 of SEQ ID NO:3 with cysteine).

Claims 30-33 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from the parent α-amylase including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in the parent α-amylase that have not been disclosed in the specification. The specification describes only a few specific variants of SEQ ID NO:3 within the scope of the instant claims. No information, beyond the characterization of these specific variants has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the function of all the polypeptide sequences derived from SEQ ID NO:3 or other related α-amylases, including variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of functions. Therefore many functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a

single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed. It is suggested that claim 30 be amended to recite "wherein said variant has α-amylase activity, has at least 80% …" in line 3.

Claims 30-33, 35 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a α-amylase having at least 90% homology to SEQ ID NO:3 and comprising a deletion of residues equivalent to 179 and 180 of SEQ ID NO:3, and substitutions of the residues equivalent to 349 and 428 of SEQ ID NO:3 with cysteine does not reasonably provide enablement for any variant of a parent α-amylase having at least 80% homology to SEQ ID NO:3 wherein said variant has at least 80% identity to said parent α-amylase and comprises deletion of residues equivalent to 179 and 180 of SEQ ID NO:3, and substitutions of the residues equivalent to 349 and 428 of SEQ ID NO:3 with cysteine The specification does not enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 30-33 are so broad as to encompass any variant of a parent α-amylase having at least 80-95% homology to SEQ ID NO:3 wherein said variant has at least 80% identity to said parent α-amylase and comprises deletion of residues equivalent to 179 and 180 of SEQ ID NO:3, and substitutions of the residues equivalent to 349 and 428 of SEQ ID NO:3 with cysteine. These genera include variants with an enormous number of alterations of the parent enzyme (which parent enzyme can be selected from an enormously large group of enzymes) and includes variants with no common function (as these claims do not require the variant to have α-amylase activity). Claims 35 and 37 are so broad as to encompass any α-amylase having at least 80-85% homology to SEQ ID NO:3 and comprising a deletion of residues equivalent to 179 and 180 of SEQ ID NO:3, and substitutions of the residues equivalent to 349 and 428 of SEQ ID NO:3 with cysteine. Thus, the currently claimed genera includes variant α-amylases with an enormous number of alterations within SEQ ID NO:3 as long as amylase activity is maintained. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variant α-amylases

broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to only a few representative species of such variant α-amylases each with only a small number of altered amino acids compared to the parent α-amylases.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish

with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any because the specification does **not** establish: (A) regions of the protein structure which may be multiply modified without effecting α-amylase activity; (B) a rational and predictable scheme for major modifications to α-amylases having 80% homology to SEQ ID NO:3 at large numbers of residues with an expectation of obtaining the desired biological function; and (C) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including an enormous number of amino acid modifications of a large number of parent α-amylases wherein said variant comprises a deletion of residues equivalent to 179 and 180 of SEQ ID NO:3, and substitutions of the residues equivalent to 349 and 428 of SEQ ID NO:3 with cysteine. The scope of the claims must bear a reasonable correlation with the

scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of α-amylases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants argue that they amended the claims as the previously suggested by the examiner. It should be noted that applicants did not in fact amend the claim exactly as suggested by the examiner, however it is acknowledged that applicants amendments are similar to the suggestion in the previous Office Action. Furthermore, while applicants have narrowed the scope of the claims in a fashion similar to what the examiner previously suggested, upon further reconsideration of the breadth of the claims as previously suggested, the examiner believes that making variants within the full scope of the current claims would still require undue experimentation. While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as α-amylases requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the

infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. While it is acknowledged that the prior art provides substantial guidance with regard to mutation of α-amylases, the instant rejected claims all include many variants with more than minor modifications to the structure of a wide variety of parent enzymes, which themselves may have substantial modifications in structural features from the enzymes which have been modified in the prior art. As such the amount of experimentation required to make and use the currently claimed scope is still deemed to be undue.

Claims 38 and 39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652